International Journal of

Innovative Drug Discovery

e ISSN 2249 - 7609
Print ISSN 2249 - 7617

www.ijidd.com

CLONIDINE VERSUS DEXMEDETOMIDINE WITH BUPIVACAINE IN CAUDAL BLOCK

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ABSTRACT

To compare the postoperative analgesic effect and side effect of clonidine and dexmedetomidine added to bupivacaine in pediatric patient undergoing lower abdominal surgery, study included 90 patients, aged 1 to 8 years scheduled for infra umbilical surgery were randomly allocated into 3 groups of 30 patients each.Induction and maintenance of anesthesia were achieved using sodium thiopental, sevoflurane and nitrous oxide. Group B received 1 ml per Kg of .25% bupivacaine, group D received 1 ml per Kg of .25% bupivacaine with 1 microgram per Kg dexmedetomidine and group C received 1 ml per Kg of .25% bupivacaine with 1 microgram per Kg clonidine .The pain score was assesed using FLACC score. Pain score was lower in group C and D as compared to group B. Addition of either dexmedetomidine or clonidine to bupivacaine significantly prolongs the post-operative analgesia time without increasing the incidence of respiratory or hemodynamic side effect.

KEY WORDS: Caudal Anaesthesia, Clonidine, Dexmedetomidine, Postoperative analgesia.

INTRODUCTION

Pain is perhaps the most feared symptoms of disease, which a man is always trying to alleviate and conquer since age. It is defined by the international association for study of pain as an "unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."[1]The human fetus is obviously incapable of verbal expression and therefore the evidence for fetal pain must be based on surrogate markers. [2] Post-operative pain has adverse psychological effect in child. Pain can result in restless and un-co-operative patient, so it is preferable to prevent the onset of pain rather than to relieve its existence. [3] Caudal analgesia is one of the most popular regional anaesthetic technique employed in children for postoperative analgesia. Gradual offset usually provides analgesia beyond the duration of surgery with a smooth recovery period and good post-operative pain control [4]. The main disadvantage of caudal anaesthesia is the short duration of action after a single injection [5]. Even long acting local anesthetic drug such as bupivacaine provides only 4-8 hrs of analgesia [6]. Prolongation of caudal analgesia using a single-shot techniques been achieved by the addition of various adjuvants such as epinephrine, opioids, ketamine, alpha2-agonist. Alpha2 – adrenergic receptor agonist like clonidine and dexmedetomidine have relevant physiological properties causing sedation and analgesia, reducing plasma catecholamine level, attenuating the stress response to surgery and preventing shivering through alpha2 adrenoreceptors in CNS [7]. This study was designed to compare the analgesic effect and side effects of dexmedetomidine and clonidine when added to bupivacaine for caudal analgesia in children undergoing lower abdominal surgeries.

EXPERIMENTAL

Paediatric patients undergoing infraumbilical surgeries fulfilling the inclusion criteria were selected for the study and randomly allocated to three different groups B, C and D of thirty each. **Group B-** Received Plain Bupivacaine 0.25 % 1 ml/ kg

Group C- Received Bupivacaine 0.25 % 1 ml/ kg + Clonidine 1 mcg/ kg

Group D- Received Bupivacaine 0.25 % 1 ml/ kg+ Dexmedetomidine 1 mcg/kg.

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Randomization was done by simple lottery method. Observer and anesthesiologist were blinded to the caudal medications administered. All medications were prepared by anesthesiologists not participating in the study except for preparing the drugs. The anesthesiologist who administered anaesthesia also monitored the patient peri-operatively, but was unaware of the study drug. Uniform technique of general anaesthesia was given. Then caudal epidural block was performed by an expert anaesthetist who was unaware of the drug used, in left lateral decubitus position using 22 gauge hypodermic needle with all aseptic precautions. The time of caudal given was noted. After identifying the sacral hiatus, a 22 G hypodermic needle with its bevel facing anteriorly was inserted at an angle of 45° to the sacrum, until bone i.e dorsal aspect of the ventral plate of the sacrum is contacted and then slightly withdrawn, and the needle is retracted so that the angle of insertion relative to the skin surface is decreased and advanced 2-3 mm to make sure that the entire bevel was inside the space. After negative aspiration for blood and CSF, to rule out intravascular or subarachnoid placement of needle, the study drug was injected according to the group allocated. After the injection was complete, the needle was removed and the child was placed in supine position. Surgical incision will be allowed 5 mins after the caudal block. No other narcotics, analgesics or sedatives were used intra-operatively. An intraoperative decrease of MAP or HR by 30% from the baseline value was defined as hypotension or bradycardia respectively and was treated by fluid bolus, ephedrine or atropine, as necessary.

At the end of the surgery reversal from general anaesthesia was done with injection neostigmine 0.04 mg/kg body weight and injection glycopyrolate 0.01 mg/kg. Patient was intubated once they are fully awake and ensuring good reflexes. Patient was shifted to post anaesthesia care unit and pain score will be assessed by using FLACC. Patients were shifted to the ward when they were 1) alert and cooperative, 2) stable hemodynamics, 3) capable of maintaining airway, 4) capable of maintaining SpO_2 more than 95% in room air.

In the post-operative period patients were monitored for adverse effect including respiratory depression, vomiting, hypotension and bradycardia. Respiratory depression was defined as SpO2 < 93% and was treated by oxygen supplementation with face mask. Hypotension was defined as systolic BP< 20% of baseline value and was treated with IV fluid bolus. Bradycardia was defined as heart rate <20% of baseline value and was treated with inj. Atropine 0.02 mg/ kg. Post-operative analgesia was assessed by using the paediatric observational FLACC pain scale with its 0–10 score range, each child's pain intensity was assessed upon arrival and then every hourly till the time of discharge from the PACU and then every 2 h for the first 24 hours after caudal block. FLACC score 0 = no pain 1-3 = mild pain 4-7 = moderate pain 8-10 = severe pain

If the FLACC pain scale score was noted at any time to be 4 or more, paracetamol syrup 15mg/kg was administered to achieve a FLACC scale score of 3 or less. The duration of adequate caudal analgesia defined as time interval between the administration of caudal block and the first requirement of supplementary analgesia for the patient was recorded.

Data entry was done using MS Excel 2007 computer software. Data were analyzed using SPSS version 20.0 computer software. Numerical variables were presented as mean and standard deviation (SD) and categorical variables were presented as frequency (%).The difference between the two groups with regards to continuous variables was assessed by Students – t test and categorical variables by chi-square test. Non parametric parameters were analyzed by Mann-Whitney Test. For all the tests a "p" value of 0.05 and less was considered for statistical significance and "p" value of 0.001 and less was considered for statistically highly significant.

RESULTS

Figure 1. The distribution of Baseline and Intra-op Heart Rate across three intervention groups.

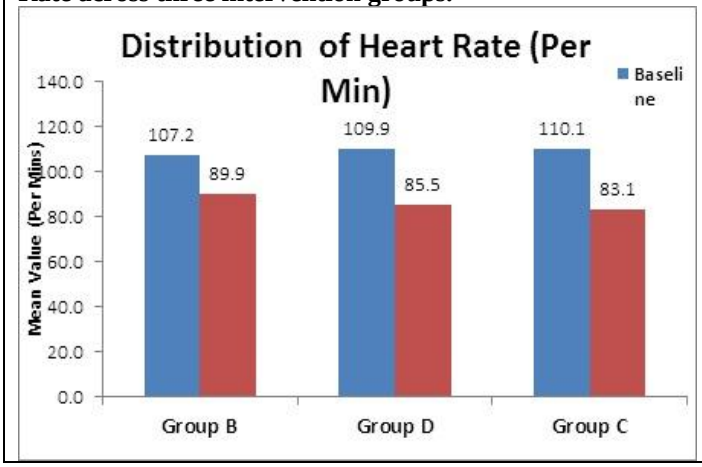

Figure 2. The distribution of baseline and intra-op MAP across three intervention groups.

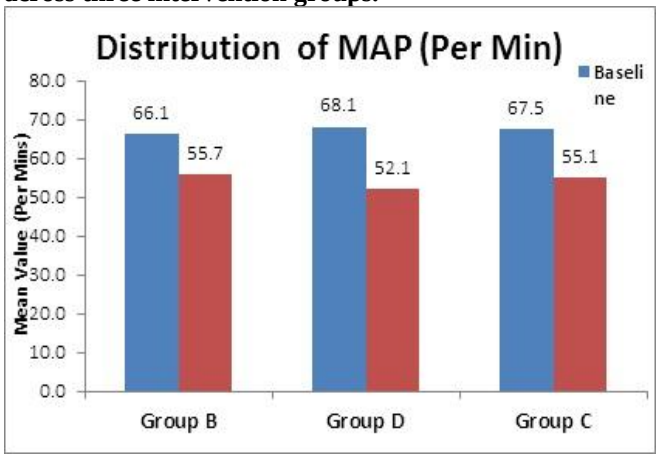

Figure 3. The distribution of Time to FLCC >4 across three intervention groups.

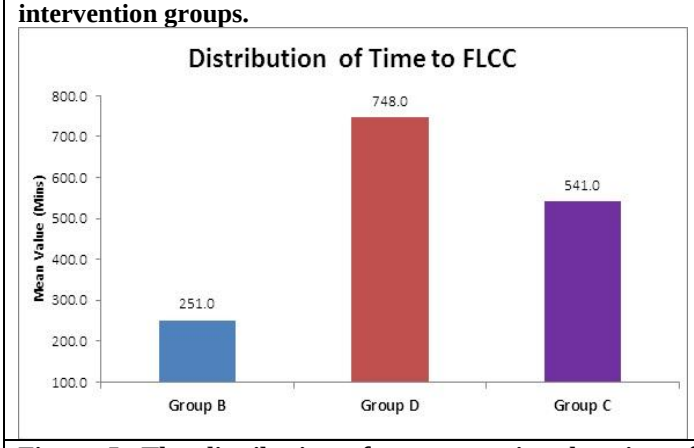

Figure 4. The distribution of incidence of Motor block across three intervention groups

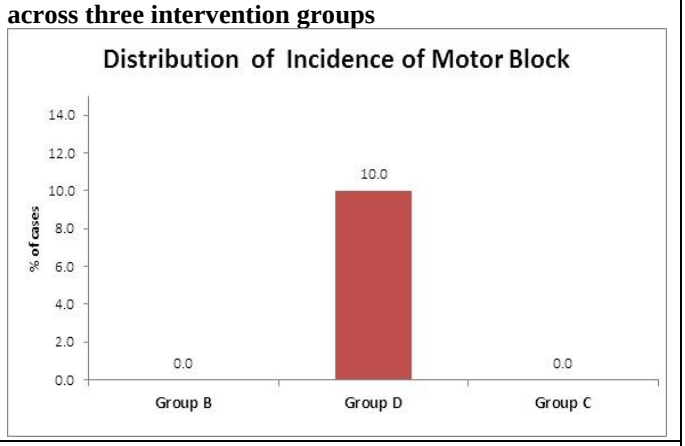

Figure 5. The distribution of post-operative duration of sedation across three groups.

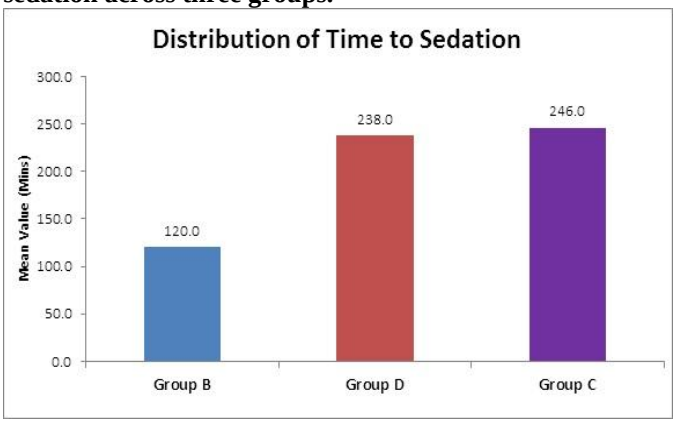

Figure 6. The distribution of complications across three intervention groups.

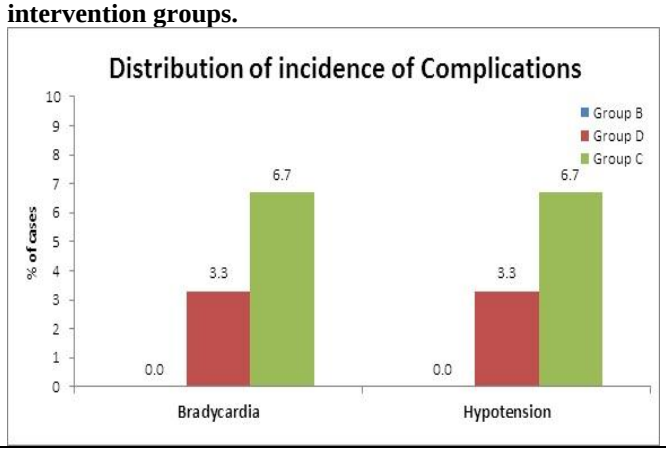

Table 1. Changes in mean heart rate across three groups

Heart Rate (Per Min)	Group B (n=30)	Group D (n=30)	Group C (n=30)	Inter-Group Comparisons (P-values)		
				Group B v Group D	Group B v Group C	Group D v Group C
Baseline	107.2 ± 14.8	109.9 ± 16.6	110.1 ± 16.4	$0.999^{(NS)}$	$0.909^{(NS)}$	$0.999^{(NS)}$
Intra-op	89.9 ± 11.9	85.5 ± 16.8	83.1 ± 16.3	$0.813^{(NS)}$	$0.257^{(NS)}$	$0.999^{(NS)}$
% Change (Intra-op)	17.4%	22.5%	24.8%	0.002^{**}	0.001^{***}	$0.357^{(NS)}$

Table 2. The distribution of baseline and intra-op MAP across three intervention groups

MAP (Per Min)	Group B (n=30)	Group D (n=30)	Group C (n=30)	Inter-Group Comparisons (P-values)		
				Group B v Group D	Group B v Group C	Group D v Group C
Baseline	66.1 ± 8.4	68.1 ± 2.5	67.5 ± 2.7	$0.429^{(NS)}$	$0.447^{(NS)}$	$0.999^{(NS)}$
Intra-op	55.7 ± 6.1	52.1 ± 3.4	55.1 ± 4.2	0.013^{*}	$0.999^{(NS)}$	0.050^{*}
% Change (Intra-op)	15.1%	23.4%	19.1%	0.001^{***}	$0.071^{(NS)}$	0.043^{*}

Table 3. The distribution of Time to FLCC >4 across three intervention groups

Time to FLCC (Min)	Group B (n=30)	Group D (n=30)	Group C (n=30)	Inter-Group Comparisons (P-values)		
				Group B v Group D	Group B v Group C	Group D v Group C
Mean ± SD Min - Max	251.0 ± 22.9 210 – 300	748.0 ± 36.0 690 – 810	541.0 ± 34.8 480 – 600	0.001^{***}	0.001^{***}	0.001^{***}

Table 4. The distribution of incidence of Motor block across three intervention groups

Incidence of Motor Block	Group B (n=30)	Group D (n=30)	Group C (n=30)	Inter-Group Comparisons (P-values)		
				Group B v Group D	Group B v Group C	Group D v Group C
Motor Block - n (%)	0	3 (10.0)	0	$0.237^{(NS)}$	$0.999^{(NS)}$	$0.237^{(NS)}$

Table 5. The distribution of post-operative duration of sedation

Time to Sedation (Min)	Group B (n=30)	Group D (n=30)	Group C (n=30)	Inter-Group Comparisons (P-values)		
				Group B v Group D	Group B v Group C	Group D v Group C
Mean ± SD	120.0 ± 0.0	238.0 ± 32.4	246.0 ± 30.9	0.001^{***}	0.001^{***}	$0.703^{(NS)}$
Min - Max	120 – 120	180 – 300	180 – 300			

Table 6. The distribution of complications across three intervention groups

Complications	Group B (n=30)	Group D (n=30)	Group C (n=30)	Inter-Group Comparisons (P-values)		
				Group B v Group D	Group B v Group C	Group D v Group C
Bradycardia	0	1 (3.3)	2 (6.7)	$0.999^{(NS)}$	$0.492^{(NS)}$	$0.999^{(NS)}$
Hypotension	0	1 (3.3)	2 (6.7)	$0.999^{(NS)}$	$0.492^{(NS)}$	$0.999^{(NS)}$

DISCUSSION

Adequate pain relief is an important aspect of postoperative care. This is important not only for the psychological well-being of the patient, but also decreases the stress response to surgery and favours a better outcome. Therefore various routes for providing pediatric postoperative analgesia were tried like: entral, parenteral, regional blocks i.e peripheral nerve blocks and central neuraxial blockade [8]. In central neuraxial blockade, safety of caudal epidural analgesia supplemented with general anesthesia, for providing intraoperative and postoperative analgesia for surgeries below the umbilicus, is well established [9]. It is easy to perform, safe, reliable, applicable to children of all ages including neonates because of prominent landmarks.

Several adjuvants have been used to prolong the duration of analgesia of caudal block using bupivacaine in children. Opioids, ketamine and midazolam are some of commonly used drugs. The use of opioids is associated with an increased incidence of pruritis and postoperative nausea and vomiting. The advantage of clonidine and dexmedetomidine is that it prolongs the duration of analgesia without an increase in the incidence of respiratory depression, pruritis and urinary retention which are commonly seen with neuraxial opioids[4].

Several mechanisms have been suggested for the clonidine-induced prolongation of caudal analgesia with bupivacaine. The anti-nociceptive action is due to the direct suppression of the spinal cord nociceptive neurons by epidural clonidine. Another mechanism is that clonidine crosses the blood brain barrier and interacts with alpha 2 adrenoceptors at spinal and supra-spinal sites to produce analgesia. Clonidine also suppresses neurotransmission in peripheral sensory A δ and C nerve fibers. The final mechanism suggested is pharmacokinetically mediated: clonidine induces vasoconstriction through α -2b adrenoceptors located at the peripheral vascular smooth muscles. [10]

Among the alpha-2 agonist clonidine and dexmedetomidine are commonly used. Clonidine has been extensively used in all type of regional anaesthetic technique. Dexmedetomidine is highly selective alpha-2 agonist especially for 2A subtype with sedative and analgesic properties and minimal respiratory depression. It is eight time more potent than clonidine. It is short acting drug than clonidine with distribution half-life of 9min and elimination half-life of 2 hours [4].

Sharpe et al. [11] speculated that a small volume of bupivacaine (0.5 ml/kg) may not be enough to deliver clonidine up to spinal cord, leaving only direct action on nerve routes in caudal area. These findings suggest that the addition of clonidine 1 mcg/kg to low volumes of caudal anaesthetic has limited clinical benefit in children undergoing in fraumbilical surgeries. This was the reason we had chosen a standard dose of 1ml/kg of 0.25% bupivacaine as the final volume in all the children of study group. Dexmedetomidine is preservative free solution and contains no additives or chemical stabilizers. In the absence of data for caudal dexmedetomidine in children, we adopted a cautious study design by using a low dose of dexmedetomidine 1 mcg/kg to avoid side effects like sedation and bradycardia. The selected caudal dose of dexmedetomidine was based on previous reports in adults.

The dose of clonidine for epidural administration is 1-5 mcg/kg. we chose a dose of 1 mcg/kg of clonidine in our study as there were study showing that increasing the dose from 1 to 2 mcg/kg did not enhance the analgesic efficiency of clonidine and incidence of adverse effects.[11] In our study we compare the duration of postoperative

analgesia between the dexmedetomidine 1 µg/kg in group D and clonidine 1 µg/kg in group C with 0.25% bupivacaine plain 1 ml/kg (2.5 mg/kg) in caudal anaesthesia in paediatric patients undergoing infra-umbilical surgeries. Study was conducted in 90 children in the age group 1- 6 yrs, of ASA status I and II coming for various infra-umbilical surgeries.

We found that the mean duration of postoperative analgesia in dexmedetomidine group was longer than the clonidine group operative period, requirement of rescue analgesic doses in the form of syrup paracetamol 15 mg/kg in 24 hours in dexmedetomidine group was less as compared to clonidine group. Our results are similar to those reported in the previous studies [4,3].

In our study, the FLACC pain scale was chosen to assess postoperative pain. The FLACC pain scale, being an observational and behavioral pain measurement score, was reliable and validated for children aged 2months to 7 years.

In 2014, Dr. Yash Meghani el al. [3] did a comparative study between caudal bupivacaine [Group A] and bupivacaine plus clonidine [Group B] for post-operative analgesia in children. The duration of analgesia in the post-operative period was more in Group B (9.98±0.86) Hrs as compared to Group A(4.3±1.12)Hrs.100% patients in Group A required two or more than two rescue analgesic within 12 hrs whereas in Group B 83% patients required single rescue analgesic and 17% required two rescue analgesic, respectively. The mean sedation scores were higher in Group B as compared to Group A.

In 2015, Dr. PS Aruna [4] studied Comparison of Plain Bupivacaine And Bupivacaine With Dexmedetomidine for Caudal Block in Children. This study was conducted among 60 children in the age group of 1 – 10 years coming for various elective infra-umbilical surgical procedures. This study showed that the addition of dexmedetomidine in the dose of 1µg/kg to 0.25% bupivacaine 1ml/kg prolonged the duration of analgesia with less post-operative analgesic requirement after a single shot caudal block with minimal side effects in children

El-Hennawy *et al* [5] Single caudal dose of bupivacaine 0.25% (1 ml/ kg) combined with either dexmedetomidine 2 µg/ kg in normal saline 1 ml in group BD, clonidine 2 µg/ kg in normal saline 1 ml in group BC, or corresponding volume of normal saline in group B. They have found that the time of adequate caudal analgesia (FLACC scale score, 4) without the need for morphine is significantly higher in the groups receiving the bupivacaine-dexmedetomidine mixture [median (95% CI):16 (14–18) h] or bupivacaine–clonidine mixture [median (95% CI): 12 (3–21) h] than the group receiving plain bupivacaine [median (95%CI): 5 (4–6) h]. They concluded that addition of dexmedetomidine or clonidine to caudal bupivacaine significantly promoted analgesia in children undergoing lower abdominal surgeries with no significant advantage of dexmedetomidine over clonidine and without an increase in incidence of side effects.

Aruna Parameshwari *et* al[11] found that the clonidine in a dose of 1 µg/kg added to 0.25% bupivacaine for caudal analgesia, during sub-umbilical surgeries, prolongs the duration of analgesia of bupivacaine (10hours) with less requirement of rescue analgesics without any side effects

In recent study done by Dipak L Raval and Kartik N [12] on efficacy of clonidine (1 mcg/kg) and dexmedetomidine (1 mcg/kg) with 0.25% bupivacaine and plain bupivacaine for caudal analgesia in children. They found that mean duration of postoperative analgesia in dexmedetomidine group was longer than the clonidine group period.

The above previous studies supported our results, adding dexmedetomidine or clonidine to bupivacaine in caudal block provides adequate intraoperative anesthesia as well as increases the duration of post-operative analgesia. The magnitude of hemodynamic changes between the two groups was similar. The episodes of clinically significant postoperative respiratory depression, hypotension, or bradycardia were not identified.

We also compared sedation with Ramsay sedation score and found that postoperative duration of sedation is higher with dexmedetomidine and clonidine. These results are statistically significant (table 5).

Considering overall incidence of side effects observed in three groups, Dexmedetomidine and clonidine was associated with lesser incidence of nausea and vomiting. The incidence of bradycardia was seen in 2 childrens in group D and 1 in group C compared to none in group B. Hypotension was observed in 2 children in group C and in 2 children in group D compared to none in group B, which is not significant statistically.

One limitation of our study was that we did not assess the mean time of arousal from anaesthesia in both the groups. The optimal dose of caudal dexmedetomidine when combined with bupivacaine is not known. Further studies are recommended to assess the effect of different doses of caudal dexmedetomidine as an adjunct to bupivacaine in caudal epidural block.

DECLARATION OF INTEREST: No conflict of interest between the Author and Co-author.

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